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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,864	10/27/2005	Peter David Davis	3963.1001-000	3397

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EXAMINER	
LAU, JONATHAN S	
ART UNIT	PAPER NUMBER
1623	
MAIL DATE	DELIVERY MODE
05/21/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/550,864	DAVIS ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2007 and 11 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24, 26-28 and 30* is/are pending in the application.

4a) Of the above claim(s) *5,6,13-15,24,26-28 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-12 and 16-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10 pgs / 26 Sep 2005, 14 May 2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is the national stage entry of PCT/GB04/01330, filed 26 Mar 2004; and claims benefit of foreign priority document UNITED KINGDOM 0306907.7, filed 26 Mar 2003; this foreign priority document is in English.

Claims 1-24, 26-28 and 30 are pending in the current application. Claims 24, 26-28 and 30, drawn to non-elected inventions, are withdrawn. Claims 5, 6, and 13-15, drawn to non-elected species, are withdrawn. Claims 1-4, 7-12 and 16-23 are examined on the merits herein.

Election/Restrictions

Applicant's election of the invention of Group I, claims 1-23, in the reply filed on 12 Dec 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

Claims 24, 26-28 and 30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12 Dec 2007.

Claims 5, 6, and 13-15 withdrawn from further consideration pursuant to 37 CFR 1.146 as being drawn to a nonelected species, there being no allowable genus claim. Election was made in the reply filed on 11 Mar 2008.

The elected species reads upon claim 12, wherein n is 0 and X is S.

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because the abstract as filed contains 202 words, as each term such as "L", "-OC(O)-", and "R_8" is interpreted as a word. Therefore the abstract exceeds 150 words in length.

Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 7-12 and 16-23 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 1 recites the terms "a **substituted** aryl or heteroaryl group," "optionally **substituted** alkyl," "optionally **substituted** alkenyl," "optionally **substituted** alkynyl," and "an optionally **substituted** heterocycloalkyl or carbocyclic ring", and the phrase "Dr is a moiety such that DrXH represents a cytotoxic or cytostatic compound". Claim 20 recites "a dolastatin **derivative**" and "a cryptophycin **derivative**".

The specification discloses chemicals, such as the compounds listed on page 15, lines 6-19 which meet the written description and enablement provisions of 35 USC 112, first paragraph. However, claims 1-4, 7-12 and 16-23 are directed to encompass substituted functional groups, "a cytotoxic or cytostatic compound" and derivatives, which only correspond in some undefined way to specifically instantly disclosed chemicals. None of these substituted functional groups meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and because substituted functional groups, "a cytotoxic or cytostatic compound" and chemical derivatives are highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus encompassed by the claim. A non-limiting definition of an alkyl, alkenyl and alkynyl substituent is provided in the specification on page 6, lines 3-15,

provided examples of groups that are included in the definition of a substituent but not limiting the definition to these examples. A non-limiting definition of an heteroaryl substituent is provided in the specification on page 7, lines 9-17. Non-limiting examples of a cytotoxic or cytostatic compound are provided on page 9, lines 26-32 and page 10, lines 1-11.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of the above specifically disclosed chemical structures, the skilled artisan cannot envision the detailed chemical structure of the encompassed derivatives, analogs, etc., regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The chemical structure itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

Therefore, only the structurally defined chemical compounds, but not the full breadth of the claims, meet the written description provision of 35 USC § 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC § 112 is severable from its enablement provision. (See Vas-Cath at page 1115.)

The court of *In re Curtis* held that "a patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when… the evidence indicates ordinary artisans could not predict the operability … of any other species." (see *In re Curtis* 354 F.3d 1347, 69 USPQ2d 1274, Fed. Cir. 2004). The court of *Noelle v. Lederman* also pointed out that generic claim to anti-CD40CR Mabs lacked written description support because there was no description of anti-human or other species Mabs, and no description of human CD40CR antigen. The court further pointed out that attempt to "define an unknown by its binding affinity to another unknown" failed. See 355 F.3d 1343, 69 USPQ2d 1508, Fed. Cir. 2004.

Dependent claims 2-11 include all limitations of claim 1 therein, and do not wholly provide sufficient description of a substituent. For example, claim 2 provides a description of an alkyl, alkenyl and alkynyl substituent, but incorporates the non-limiting description of an aryl, heteroaryl, heterocycloalkyl ring and carbocyclic ring substituent and a cytotoxic or cytostatic compound defined in the specification. For example, dependent claim 20 provides a description of a cytotoxic or cytostatic compound but incorporates the non-limiting description of a substituent.

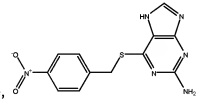
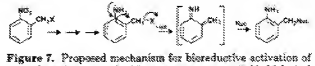
Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

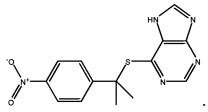
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

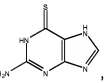
Claims 1-4, 7-12 and 16-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirkpatrick et al. (J. Med. Chem. 1986, 29, p2048-2052, cited in PTO-892) as evidenced by Teicher et al. (J. Med. Chem. 1980, 23, p955-960, cited in PTO-892), in view of Streitwieser et al. (Introduction to Organic Chemistry, 4th ed, 1992, p 192-197, cited in PTO-892) and in view of Krynetski et al. (Molecular Pharmacology, 1995, 47, p1141-1147, cited in PTO-892).

Kirkpatrick et al. discloses nitrobenzyl derivatives as bioreductive alkylating agents, such as (nitrobenzyl)thioguanine (page 2048, spanning left column, paragraph 3 and right column, paragraph 1). Such compounds are exemplified on page 2051 in table IV, S-(*p*-nitrobenzyl)-6-thioguanine,  . Kirkpatrick et al. discloses the compound in a pharmaceutically acceptable composition with dimethylsulfoxide and ethanol, pharmaceutically acceptable carriers (page 2052, right column, paragraph Biological Methods). Kirkpatrick et al. discloses the thioether linkage is stable under bioreductive conditions (page 2051, spanning left column, paragraph 5 and right column, paragraph 1). Teicher et al., reference 15 of Kirkpatrick et al., provides evidence that it was known in the prior art that the proposed mechanism of the reduction of the nitrobenzyl group, 
Figure 7. Proposed mechanism for bioreductive activation of o-nitrobenzyl compounds. Nuc represents any available biological nucleophile.
is an S_N1 type mechanism (Teicher et al. page 959, left column, Figure 7). One of skill in the

art would instantly understand that the mechanism is the same for a *p*-nitrobenzyl compound disclosed by Kirkpatrick et al. based on the aromaticity of a phenyl ring.

Kirkpatrick et al. does not disclose the compound 6-(2-(4-nitrophenyl)propan-2-ylsulfanyl)-9H-purine,  .

Streitwieser et al. teaches that in an S_N1 mechanism a tertiary alkyl group reacts faster than a primary alkyl group (page 195, 2nd full paragraph and summary table). Streitwieser et al. teaches that increasing the number of methyl group substituents to increase the stability of the carbocation intermediate and therefore the reactivity of the starting material. (page 195, 1st full paragraph and table 9.7).

Krynetski et al. teaches mercaptopurine,  , and thioguanine,  , are art recognized equivalents known for the same purpose, prodrugs converted to cytotoxic thiopurine nucleotides (page 1141, left column, paragraph 1). Krynetski et al. teaches the mechanism of action of the compounds is known to be equivalent (page 1141, figure 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the compound disclosed by Kirkpatrick et al. with the teaching of Streitwieser et al. the teaching of Krynetski et al. Krynetski et al. teaches

mercaptopurine and thioguanine are art-recognized equivalents known for the same purpose, with closely related chemical structures and a similar mechanism of action. It is *prima facie* obvious to substitute mercaptopurine for the thioguanine of the compound disclosed by Kirkpatrick et al., An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious, see MPEP 2144.06 II. One of ordinary skill in the art would be motivated to combine the teaching of Streitwieser et al. of increasing the number of methyl substituents of a carbocation with the compound taught by Kirkpatrick et al. in view of Krynetski et al. because Streitwieser et al. teaches that increasing the number of methyl group substituents increases the reactivity of the starting material and Kirkpatrick et al. discloses the thioether linkage is not reactive under bioreductive conditions. One of ordinary skill in the art would have a reasonable expectation of success in combining the teaching of Streitwieser et al. with the compound taught by Kirkpatrick et al. in view of Krynetski et al. because the effect of alkyl substitution on the reactivity of carbocations is well-established in the field of organic chemistry.

Conclusion

No claim is found to be allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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